

REVIEW

Inpatient management of hepatic encephalopathy

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INTRODUCTION

Hepatic encephalopathy (HE) in patients with liver cirrhosis is caused by chronic liver dysfunction and various degrees of portosystemic shunting. Approximately half of patients with liver cirrhosis will experience one or more episodes of HE during their disease course, and it could be the first complication in 10%–15%.^[1] Consequently, HE is often the primary or adjacent clinical problem during hospital admission. The first HE episode comes with an increased risk of recurrence of 40% within a year and a poor prognosis, with only ~35% of patients being alive after 1 year.^[1] Accordingly, HE always requires multiple actions beyond anti-HE treatment. Here, we outline the most crucial steps to take and considerations to make upon a clinical encounter with mental status changes in an inpatient with cirrhosis.

THE INITIAL APPROACH TO MENTAL STATUS CHANGES IN AN INPATIENT WITH CIRRHOSIS

HE is the most important differential diagnosis in patients with liver cirrhosis presenting with altered mental status. Nevertheless, other causes or contributors to the symptoms should always be considered, managed, or excluded (Figure 1). The initial step is a Glasgow Coma Scale rating and a thorough neurological exam to determine the symptoms' severity and narrow the list of differential diagnoses. Although imaging cannot securely diagnose HE, appropriate brain and cranial imaging may be needed to exclude important diagnoses, including

intra-cranial diseases such as acute and chronic subdural hematoma, subarachnoid bleeding, stroke, and neuro infection. Imaging is especially useful in the case of focal neurological signs or at the first presentation of altered mental status in cirrhosis. In patients who are comatose or stuporous, the fastest imaging modality should be preferred, which, in most emergency departments, is a CT scan. Initial blood tests should be a broad screening to assess the status of known comorbidities and a regular work-up for electrolyte disorders, infections, and other potential causes of altered mental status. The serum sodium level is particularly interesting as sodium is an independent driver of HE, and if it is low, it should be corrected.^[2] Further, as patients with cirrhosis are immunosuppressed, infections are the most common cause of hospital admission in cirrhosis and a common precipitating factor for HE. Therefore, blood culture, ascites, and urine investigations for infections such as spontaneous bacterial peritonitis should be prioritized. Stool and tracheal secretion culturing should be performed at the slightest clinical suspicion of gastroenteritis and pneumonia. Erysipelas/cellulitis is not uncommon in cirrhosis and should be a focus of the physical examination. The same applies to oral infections, including fungal infections; thus, the oral cavity should always be inspected. Lastly, a urine drug screen is needed to exclude opioid and benzodiazepine intoxication.

If the neurological examination, CT, and biochemistry cannot create sufficient diagnostic certainty, lumbar puncture and electroencephalography may be needed to exclude viral, bacterial, or fungal meningitis and epileptiform disease. Delirium tremens caused by untreated alcohol withdrawal symptoms and psychiatric

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ANT, Animal Naming Test; EASL European Association for the Study of the Liver; HE, hepatic encephalopathy; WHC, West Haven Criteria.

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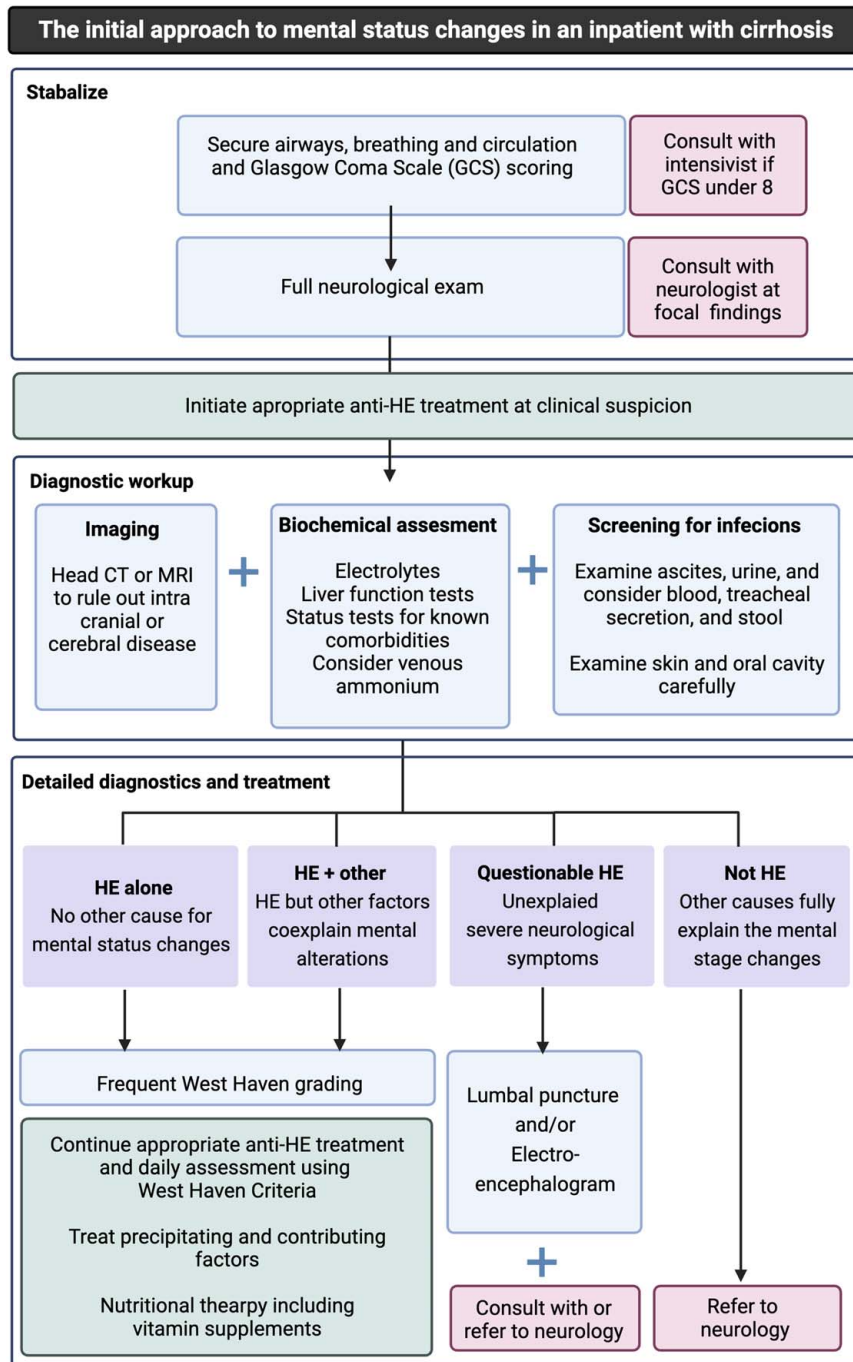


FIGURE 1 Overview of the initial clinical approach to a patient with cirrhosis admitted to the hospital due to mental state changes. Abbreviation: GCS, Glasgow Coma Scale.

disorders are also important differential diagnoses to consider. In the meantime, treatment for HE can be initiated based on clinical suspicion.

Role of ammonia

Ammonia is produced in various organs, including the small intestine and kidneys, and is eliminated at a lower

rate in liver insufficiency. It readily crosses the blood-brain barrier, acts as a neurotoxin, and is a driver of HE, sarcopenia, and immune dysfunction.^[3] Venous ammonia measurement can be used as a confirmatory test in HE grades 3 and 4 but is generally poorly correlated to HE grade.^[4] The HE diagnosis is questionable if a patient is stuporous or comatose and ammonia is normal. Conversely, if ammonia is normal in patients with milder mental changes, this does not rule out HE as a cause of these

changes. Hence, venous ammonia can be used for guidance in severe mental changes but is not a diagnostic test for HE.^[5]

APPROACH IF HE IS ESTABLISHED AS THE SOLE OR PARTIAL CAUSE OF THE MENTAL STATUS CHANGE

If no other cause can fully explain the observed mental state changes and/or ammonia is elevated, HE is assumed to be the main explanatory factor (Figure 1). HE is an organic delirium, and symptoms are as such reversible and appear earlier in persons with a poor cognitive reserve (elderly, comorbid, prior HE or organic brain disease such as dementia). Symptoms can fluctuate within a few hours and are graded using the West Haven Criteria [(WHC) Figure 2]. Grading is performed daily in admitted patients with WHC grades 1 and 2 but more frequently in grades 3 and 4.^[4] Regardless of WHC grade, the daily patient evaluation should include a crude neurological examination. In WHC grades 1, 2, and 3, latency/slow cerebration is a hallmark symptom, and here, the animal naming test (ANT), which assesses verbal fluency, can be useful as a quick and reproducible psychometric test to quantify mental impairment. The ANT is performed by asking the

patients to name as many animals as possible within a minute. It is important to note that ANT normal values vary between counties and regions, but even if normal values are not locally established, ANT can be used to access a single patient's progress from day to day. A handful of more advanced psychometric tests exist for diagnosing and grading subclinical symptoms of HE and are used in the outpatient setting.^[6]

INPATIENT MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Regardless of HE severity, treatment in the inpatient setting rests on 3 main pillars: Treatment of the precipitating factor, anti-HE treatment, and nutritional therapy (Figure 1). In addition, it must be ensured that iatrogenic worsening of the patient's condition by complications such as aspiration pneumonia, falls, and hyponatremia due to dehydration are avoided. In patients with ongoing alcohol overuse, it is further essential to remember treatment for alcohol withdrawal symptoms, which can exacerbate mental impairment and render the patient uncooperative. In patients with HE WHC grade 3 or 4 observations, sometimes intubation in the stepdown or intensive care unit is appropriate due to the risk of aspiration.

West Haven Criteria in the Grading of Hepatic Encephalopathy					
Grade 0	Minimal HE	Grade 1	Grade 2	Gade 3	grade 4
Unimparied	Covert HE		Overt HE		
Not hospitalized			Hospitalized		
Detectable with psychometric tests		Clinically detectable			
Appears unimparied and is tested and found unimparied	Abnormal results at psychometric testing Most widely used test is portosystemic encephalopathy syndrome (PSE) test.	Trivial lack of awareness Shortened attention span Subtle chanes to personality Altered sleep rythm	Latency Porfound personality changes Dyspraxiia Disorientation for time Apathy	Bizarre behavior Gross disorientation Confused Semistupor Somnolence	Comatose
Clinical assessment method					
Psychometric testing Statement from caregiver that patient acts normal Is responsive and can follow line of conversation	Psychometric testing	Casual conversation reveals inattentiveness, slight latency, problems following conversation as usual Caregiver observations	Disorientation for time and fails to name at least three of the following: date, weekday, month, season, and year	Also disorientation for more place and fails to name three of the following: Country, state/region, city, and place	Does not respond to painfull stimuli

FIGURE 2 The West Haven Criteria are used for the grading of HE, and the figure shows symptoms and suggested methods of clinical assessment for each West Haven Grade. Abbreviation: PSE, portosystemic encephalopathy syndrome.

The most frequent precipitating factors include infections, dehydration, variceal bleeding, and constipation, often accompanied by severe nutritional problems, including vitamin deficiencies. A tailored treatment plan based on the prevailing guidelines for each precipitating factor and the patient's individual needs must be devised as soon as possible. Focus on nutrition using dietician colleagues is associated with better outcomes in hospitalized patients with cirrhosis.^[7]

HE treatment is cheap and effective because nonabsorbable disaccharides such as lactulose are first-line therapy and will improve mental state if dosed and monitored appropriately.^[8] Lactulose acts in the gut where it, apart from ensuring bowel movements, lowers stool pH and is thereby believed to promote a favorable microbiome composition and lower endotoxin load. In WHC grades 3 and 4, this should be given through an enema rather than orally to prevent aspiration. A lactulose enema can be substituted by polyethylene glycol in case of persistent constipation or sub-ileus or if the patient is unable to tolerate lactulose. Lactulose treatment improves HE with a low number needed to treat of 4 and prevents recurring HE (number needed to treat = 6).^[9] Rifaximin, a gut-acting antibiotic, is the second-line therapy in HE nonresponsive to lactulose and has been reported to lower the risk of HE recurrence by almost 25%.^[10,11] Other medications

such as branched-chain amino acids (aid the skeletal muscles' detoxification of ammonia) and L-ornithine L-aspartate (enhances glutamine synthesis in the liver and thereby aids elimination of ammonia) are third-line therapies.

In very few cases, the standard treatment is ineffective, and this should prompt an eager search for initially overlooked causes for mental state alterations, including hepatic myelopathy or hepatic parkinsonism, which are not responsive to anti-HE treatment.^[8] If HE is persistently above WHC grade 2 despite therapy, the diagnosis of HE should be questioned, the list of possible precipitating factors should be revisited, and undiagnosed or inadequately treated factors such as portosystemic shunts (TIPS or spontaneous), and resistant infections should be managed. A brain MRI could be indicated to evaluate the cerebral parenchyma in detail and will inform clinicians of signs of Alzheimer, smaller prior strokes, tumors, and encephalitis that may explain or contribute to mental changes unresponsive to standard treatment. A handful of ammonia-scavenging drugs may also have a place in these cases but are only used off-label in special cases, as none are yet approved for HE treatment. The ultimate treatment for HE is a liver transplant in eligible patients. Unless HE is seen as a part of terminal liver failure, anti-HE treatment and

Points to consider at discharge of a patient admitted with hepatic encephalopathy		
Information	Chart Review	Planning the Future
Oral and written to patient Description of events during the admission Symptoms and signs that should prompt renewed contact with healthcare professionals How to take and titrate lactulose Self-management advice such as diet Place, time and date for follow-up Family and professional caregivers Share all information if approved by the patient	List of medications Proton pump inhibitors: Stopped if not solid indication Opioids and benzodiazepins: Titrated to smallest possible dose or stopped Lactulose: Ensure right dose and that HE is listed as the indication Nutritional supplements: Order at least one protein drink before bedtime Non-selective beta-blockers: Consider dose reduction in case of hyponatremia, low blood pressure or impaired kidney function	Consider early or late palliative care interventions Consider liver transplant listing Establish at-home assistance Initiate alcohol treatment 2 - 4 weeks followup Psychometric testing Ensure anti-HE treatment compliance Debriefing — HE is a frightening experience for patient and caregiver

FIGURE 3 Points to consider at discharge of a patient admitted with hepatic encephalopathy.

treatment of precipitating factors will cause improvement in mental state within hours to a few days. The approach towards HE outlined here is the same regardless of other organ failures and in acute-on-chronic liver failure.

CONSIDERATIONS AT DISCHARGE

There are several important points to consider at discharge, and the goal is to avoid preventable readmissions and to optimize the patient's quality of life (Figure 3). Often, patients remember very little of an HE episode, which can cause a deep sense of loss of autonomy and shame. Education is of utmost importance and should include a written layman's description aimed at the patient and caregivers describing the inpatient events. The information should also include advice on self-management of the disease (dietary advice, alcohol cessation), the importance of adherence to the medical regimen, and the signs and symptoms that should prompt renewed contact with health care professionals, such as recurrent HE, constipation, or diarrhea. Lastly, an appointment for follow-up should be planned. Before discharge, the list of medications should be thoroughly reviewed in collaboration with the patient. If possible, proton pump inhibitors should be stopped, and benzodiazepines and opioids should be tapered to the smallest possible dose and preferably stopped if possible. The patient should be carefully instructed in lactulose titration according to bowel movement number and consistency, and if not capable, assistance should be ensured.^[12–14] Nonselective beta-blocker dose should be reduced if hyponatremia is present or kidney function is impaired to prevent the worsening of HE. Continuous confirmation of adherence to the prescribed pharmaceuticals and supplements should be highly prioritized at follow-up visits, and causes for noncompliance should be identified. This includes securing proper access to refills, addressing any side effects, and keeping track of unfavorable prescriptions made in other departments. If there is evidence of frailty, sarcopenia, or a high fall risk, an evaluation by a physiotherapist and nutritional service is needed to prevent these outcomes and to improve nutrition. Also, consuming a snack or protein drink before nighttime is advisable to prevent catabolism. Mental health and/or addiction therapy is essential for patients with alcohol-associated liver cirrhosis and ongoing use. HE-related hospital admission should further result in considerations on eligibility for liver transplantation, and if ineligible, early palliative care in parallel to active treatment should be offered. As such, it takes a multidisciplinary effort and coordination to properly steer patients clear of further adverse outcomes and maintain the highest possible quality of life.^[15] Failure to implement such efforts is the reason for preventable readmissions and reduced quality of life and explains

why health care expenses for HE management exceed those for cardiac failure and chronic pulmonary disease.^[16]

Other educational resources related to HE can be found here:

- EASL/AASLD practice guidelines for HE management in chronic liver disease.^[5]
- Important unresolved questions in the management of hepatic encephalopathy: An ISHEN Consensus.^[17]
- EASL Clinical Practice Guideline based on a 2022 Delphi panel process is available here.^[18]
- Nature Reviews Disease Primers Hepatic Encephalopathy, 2022^[4]

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CONFLICTS OF INTEREST

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